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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,266	01/27/2004	Reuel B. Van Atta	NX#26	3800

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EXAMINER
SHAW, AMANDA MARIE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,266	VAN ATTA ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 33-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-32 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group II in the reply filed on April 28, 2006 is acknowledged. The response did not specifically traverse the restriction requirement. It is also noted that the applicant further elected the point mutation (G845A) in the HFE gene for prosecution. Accordingly, Claims 23-32 and 41-46 have been examined herein.

Additionally it is noted that the Applicant elected SEQ ID NO:29 for the prosecution of Claim 44 over the phone on May 8, 2006.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-32 and 41-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-32 and 41-44 recite the limitation "the normal nucleic acid. There is insufficient antecedent basis for this limitation in the claim.

Claims 24-32 and 41-44 are indefinite because claim 24 recites the phrase "the normal nucleic acid". This phraseis considered indefinite because it is unclear as to what a normal nucleic acid is. This phrase is not defined by the claim or the specification, and one of ordinary skill in the art would not be reasonably apprised of the

scope of the invention. While page 2 of the specification provide an example of what is considered abnormal, a complete definition for normal is not provided. The specification provides examples of what is abnormal (i.e. deletions and duplications, substitutions, insertions, translocations, rearrangements, variable number of tandem repeats, short tandem repeats, retrotransposons such as Alu and long interspersed nuclear elements, and the like). There for it is unclear if the claims which recite "the normal nucleic acid" include every nucleic acids which lacks a deletions and duplications, substitutions, insertions, translocations, rearrangements, variable number of tandem repeats, short tandem repeats, retrotransposons such as Alu and long interspersed nuclear elements, and the like. Since the specification only defines abnormal it is unclear how normal should be interpreted. Therefore the teachings in the specification are not considered to be sufficient to provide a complete and fixed definition for the phrase "the normal nucleic acid." Additionally the claims are indefinite because claim 24 recites the phrase "a method according to claim 23 comprising an additional capture probe ". This language is unclear because a method can not comprise a product, it can only comprise a step that utilizes a product. The claim should recite how the additional capture probe is used in the method (e.g., the method according to claim 23 wherein an additional capture probe is used to hybridize to the portion lacking said polymorphism).

Claims 25-32 and 41-44 are indefinite because claim 25 recites the phrase "a method according to claim 24 additionally comprising a reporter moiety". This language is unclear because a method can not comprise a product, it can only comprise a step that utilizes a product. The claim should recite how the reporter moiety is used in the

method (e.g., a method according to claim 24 wherein the capture probe comprises a reporter moiety).

Claims 28 and 29 recite the limitation "the crosslinking compound". There is insufficient antecedent basis for this limitation in the claim.

Claim 32 is indefinite because the claim recites the phrase "a method according to claim 30 comprising a fluoresceinated reporter molecule". This language is unclear because a method can not comprise a product, it can only comprise a step that utilizes a product. The claim should recite how the fluoresceinated reporter molecule is used in the method (e.g., a method according to claim 30 wherein a fluoresceinated reporter molecule is used to hybridize to said target sequence).

Claims 42-44 are indefinite because claim 42 recites the phrase "the method of claim 41 comprising a first capture probe....". This language is unclear because a method can not comprise a product, it can only comprise a step that utilizes a product. The claim should recite how the probes are used in the method (e.g., the method of claim 41 comprising a first capture probe, a second capture probe, a first flanking probe and a second flanking probe which are used to hybridize to said target sequence). Additionally it is unclear if these probes also used in the assay in addition to the ones recited in claim 25 or if the claim is intended to further defined the each of the probes. The rejection can be overcome by amending the claim to recite, e.g., "the method of claim 41 wherein the first capture probe has the sequence of SEQ ID NO: 25, the second capture probe has the sequence of SEQ ID NO: 26 .....".

Claim Rejections - 35 USC § 103

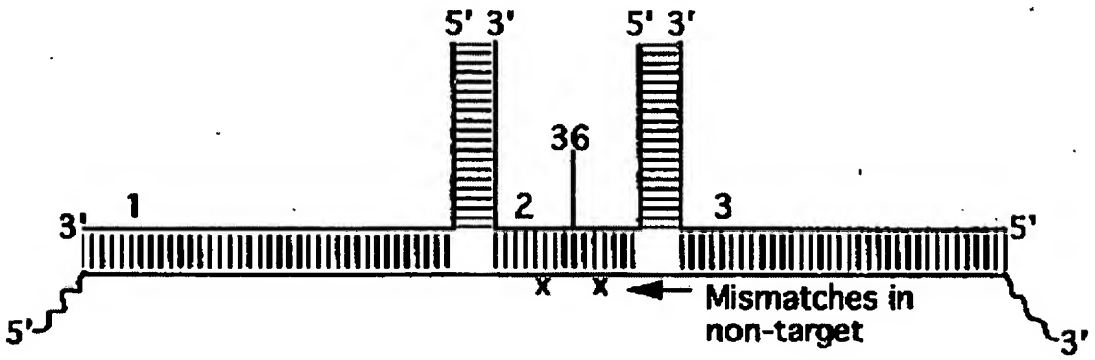
3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-31 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al (US Patent 5424413) in view of VanAtta (WO 01/79563).

Hogan et al teach a method for detecting a genetic polymorphism in a target nucleic acid sequence comprising: combining a target nucleic acid and a plurality of probes under hybridizing conditions wherein the plurality of probes comprises a) a first flanking probe comprising i) a sequence substantially complementary to a first portion of said nucleic acid sequence, and ii) a first side chain, b) at least one capture probe comprising i) a sequence substantially complementary to a second portion of said nucleic acid sequence, said second portion comprising the location of said polymorphism, said second portion being adjacent to said first portion, ii) a second side chain substantially complementary to said first side chain, and iii) a third side chain and c) a second flanking probe comprising i) a sequence substantially complementary to a third portion of said target nucleic acid sequence, said third portion being adjacent to said second portion, and ii) a fourth side chain substantially complementary to said third side chain, wherein said first and second side chains and said third and fourth side chains non-covalently bind to form first and second stems, respectively, upon base

pairing of said probes to said target nucleic acid sequence (See Below, Figures 6a-6c, and Example 3).



Hogan et al do not teach a method wherein at least one of said first and second side chains and at least one of said third and fourth side chains comprises an activatable crosslinking group, which upon activation forms a covalent cross-link with the other side chain comprising said stem, and wherein at least one of said first and second flanking probes comprises, in the sequence which is substantially complementary to its respective portion of said nucleic acid sequence, an activatable crosslinking group which upon activation forms a covalent crosslink with said respective portion comparing the degree of hybridization of said capture probe to said sequence portion containing said polymorphism to the hybridization of a capture probe to said target sequence lacking said polymorphism whereby the polymorphism is determined.

However, it was well known in the art at the time of the invention that nucleic acids could be crosslinked to form an irreversible hybrid. Specifically VanAtta teach two

nucleic acid probes that form stem regions that are crosslinked (Page 6). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hogan et al so as to have crosslinked the nucleic acids in order to have achieved the benefits set forth by VanAtta of providing a method which allows for a irreversible probe-target hybrid. Irreversible hybrids are beneficial because they provide increased signal as a result of more efficient target capture and decreased back ground as a result of more effective removal of nonhybridized probes.

Regarding Claim 24, Hogan et al teaches the use of an additional probe which is complementary to the wild type sequence. Specifically Hogan teaches the use of branched nucleic acid probes to detect a variety of targets with related but non-identical sequences. For example, Hogan teaches an exact target probe (78 bp) that is specific to a region of the gag gene in HIV-1. Hogan also teaches additional probes (also 78 bp) that contain a variety of mismatches to the same region of the gag gene in HIV-1 (Example 7).

Regarding Claim 25, Hogan et al teaches that the probe additionally comprises a reporter moiety with a detectable label. The preferred method of detection utilizes a chemiluminescent acridinium ester (AE) label covalently attached to an oligonucleotide probe. Additional types of detectable labels are also contemplated (Column 6).

Regarding Claims 26-29, VanAtta et al teaches a method wherein the crosslinking group is photoactivatable (i.e. coumarin, furocoumarin or psoralen) and the crosslinking compound is O-(7-coumarinyl) glycerol. Specifically VanAtta teaches crosslinking compounds that are non-nucleosidic, stable, photoactive compounds that

comprise coumarinyl derivatives. Examples of crosslinking compounds that react with crosslinking compound reactants such as modified or unmodified pyrimidine nucleosides or derivatives are coumarin derivatives including (1) 3-O-(7-coumarinyl) glycerol; (2) psoralen and its derivatives, such as 8-methoxypsoralen or 5-methoxypsoralen; (3) cis-benzodipyrone and its derivatives; (4) trans-benzodipyrone; and (5) compounds containing fused coumarin cinnoline ring systems. All of these molecules contain the necessary crosslinking group located in the right orientation and at the right distance to crosslink with a nucleotide. In addition, all of these molecules are coumarin derivatives, in that all contain the basic coumarin ring system on which the remainder of the molecule is based (Pages 6 and 7).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hogan et al so as to have crosslinked the nucleic acids using a photoactivatable crosslinking group (i.e.coumarin, furocoumarin or psoralen) and the crosslinking compound is O-(7-coumarinyl) glycerol since these reagents were well known in the art at the time of the invention and typically used to perform crosslinking reactions.

Regarding Claim 30, Hogan et al teaches a method wherein the polymorphism being detected is a SNP. Specifically Hogan et a teach that the second probe contains a region that is capable of binding to the target nucleic acid. The region may contain one (such as a SNP) or more mismatches to the target nucleic acids. This probe segment will form a stable duplex with perfectly matched target, but will not form a stable duplex with mismatched targets (Column 15).

Regarding Claim 31, VanAtta teach a method wherein capture probes are biotinylated. Specifically VanAtta teach that the capture probe is labeled with a capture moiety (i.e. biotin) which causes the binding of the probe onto a solid support containing avidin or streptavidin. The capture of the product occurs since the capture group is linked to the product (Page 10).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hogan et al so as to have attached a biotin molecule to one of the probes in order to have achieved the benefits set forth by VanAtta of providing an effective way of isolating the capture probe and the target nucleic acid. The method of VanAtta allows for the isolation of the capture probe and the target nucleic acid because the capture probe is hybridized to the target and has a biotin attached to it. When it comes in contact with a solid support which has streptavidin or avidin on it, the biotin will bind to it and everything else can be washed away thus isolating the capture probe and the target.

Regarding Claims 45-46, Hogan et al teach that the probes can be RNA or DNA (Column 6).

4. Claim 32, 41, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al (US Patent 5424413) in view of VanAtta (WO 01/79563) and in further view of Wylenzek (Clinical Chemistry).

The teachings of Hogan et al and VanAtta et al are presented above.

The combined references do not teach fluoresceinated reporter molecules which hybridize to the target nucleic acid sequence.

However Wylenzek et al teach fluoresceinated reporter molecules which hybridize to the target nucleic acid sequence (Page 1854).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hogan et al so as to have used a fluoresceinated reporter molecule which hybridizes to the target nucleic acid sequence instead of using a probe covalently attached to acridinium ester because fluoresceinated reporter molecules provide an equally effective means for detecting the hybridization complex.

Regarding Claim 41 Hogan et al and VanAtta do not teach a method wherein the polymorphism being detected is a point mutation (G845A) in the HFE gene.

Wylenzek et al teach a method which is used to screen for the Cys282Tyr mutation of the HFE gene. This mutation is caused by a point mutation that occurs at nucleic acid position 845 and changes a G→A.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hogan et al so as to have used probes to determine the nucleic acid at position 845 of the HFE gene because this gene is the primary disease causing mutation of hereditary hemochromoatosis. The benefit of determining the genotype is that early diagnosis and therapy can entirely prevent clinical complications.

5. Claims 42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al (US Patent 5424413) in view of VanAtta (WO 01/79563), in further view of Wylenzek (Clinical Chemistry), and in further view of Feder (Nature Genetics) .

The teachings of Hogan, VanAtta, and Wylenzek are presented above.

The combined references do not teach a method using a probe set comprising a first capture probe having the sequence of SEQ ID NO: 25 a second capture probe having the sequence of SEQ ID NO: 26 a first flanking probe having the sequence of SEQ ID NO: 27 and a second flanking probe having the sequence of SEQ ID NO: 28 and further a reporter probe consisting of SEQ ID NO:29.

However, Feder et al teach the full length mRNA sequence of the HFE gene (Accession # U60319). The target specific regions of the disclosed sequences of SEQ ID Nos. 25-29 are complementary to the full length sequence taught by Feder. For example SEQ ID No: 25 and 26 are complementary to nucleotides 1060-1074 in the Feder reference, SEQ ID No: 27 is complementary to nucleotides 1028-1057 in the Feder reference, and SEQ ID No: 28 is complementary to nucleotides 1075-1110 in the Feder reference. Please note that SEQ ID No: 25-28 contain regions that are not complementary to the target but are complementary to the other probes. For example the 3' "anaa" region of SEQ ID No: 25 and 26 forms a stem region with the 5' "tttt" region of SEQ ID No: 27. Additionally the 5' "ttt" region of SEQ ID No: 25 and 26 forms a stem region with the 3' "ana" region of SEQ ID No: 28.

While the combined teachings do not teach the exact probes of SEQ ID Nos: 25-29, the generation of probes for the detection of the point mutation G8458 using the

method of Hogan would have been obvious to one of ordinary skill in the art at the time the invention was made. Detection of mutations using hybridization probes which form branched nucleic acid structures was well known in the art at the time the invention. Hogan et al teach that when designing branched probes such as the one presented above the target specific region of the first and second flanking probes should be relatively long and therefore form stable duplexes with target and even closely related non-target nucleic acids that possess homologous sequences in these regions. The target specific region of the capture probe should be relatively short, and span a region that contains one or more mismatches to non-target nucleic acids. This probe segment will form a stable duplex with perfectly matched target, but by virtue of its relative shortness will not form a stable duplex with mismatched targets (Column 15). The stem regions are also important because the Tm of the arm region is much lower in the absence of target than in the presence of target, and the duplex regions formed between the target and the probe are less stable in the absence of the arm structure. Hogan et al teach that the stem region can made up of any complementary base pairs. Designing probes which are equivalents to those taught in the art is routine experimentation. The parameters and objectives involved in the selection of probes were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum probes. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design probes which can form branches. Additionally the full length sequence for the HFE gene was

well known and it would be obvious to choose the probes of the present invention because the flank the mutation site. One skilled in the art should have been able to design a probe set containing probes comprising a first region with a sequence complementary to the target and a second region with a sequence complementary to another probe so that the two probes can form a stem region (i.e. this sequence is not from HFE). Thereby for the reasons given above designing the probes of SEQ ID Nos: 25-29 would have been obvious.

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634
May 15, 2006

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER